REMARKS

Claims 1-8 are currently pending in the subject application. Applicants have amended claims 1, 5 and 7.

Rejections Under 35 USC 112 first paragraph

Claims 1-9 and 84-85 were rejected under 35 USC 112 first paragraph as allegedly failing to comply with the written description. Specifically, the Examiner asserted that the specification is drawn to the use of specific Epstein Barr virus and allegedly "does not provide adequate support regarding the open ended method of using survival plasmid to screen synthetic lethality in mammalian cells".

In response, Applicants traverse the Examiner's assertion:

The method used by the Applicant can be performed by any one who is skilled in the art, according to the description provided and exemplified by Applicants with any "plasmid that is autonomously replicating and spontaneously lost from said cell". The EBV-based vector that employed in the subject application is a representative vector of a group of emerging plasmid episomes of either human or viral origin. Applicants have used EBV-based replicon over for example, the Bovine Papilloma Virus (BPV) replicon, because their studies have shown low level of stochastic integration of the former, whereas the latter is notorious for episomal state loss through stochastic integration.

Rejections under 35 USC 112 second paragraph

The Examiner asserted that Claim 1 step viii, is being indefinite for failing to particularly point out and distinctly claim the subject matter, which applicants regard as the invention. In addition, the Examiner asserted that Claim 1 line 1 has to be amended.

In response, Applicants have amended the typographical errors in Claim 1 step viii and in claim 1 line 1.

The Examiner further asserted that Claims 5 and 7 have insufficient antecedent basis for the limitation in these claims or in claim 1 on which they are dependent upon.

In response Applicants have amended the typographical errors in Claims 5 and 7.

Lastly, the Examiner asserted that Claim 1 is allegedly incomplete for allegedly omitting essential steps. According to the Examiner, the claimed method recites a method for screening a molecule –however, the Examiner asserted that the claimed method does not recite whether the molecule to be screened is transfected into a vector. According to the Examiner, the instant claimed method recited that the molecules are added to the survival plasmids selected in step vii. Further, the Examiner's asserted that the method seems to be allegedly missing a method of "how a molecule having a synthetic lethal property is identified by determining the survival plasmid".

In response, applicants traverse the Examiner's assertion. The screened molecules are not transfected into vectors. The molecules, which are chemical compounds or drugs are indeed simply added to cells that were previously selected.

The Examiner further asserted that the method seems to be missing a step specifically, the Examiner asked "how a molecule having a synthetic lethal property is identified by determining the survival plasmid".

In response, in order to further clarify the invention Claim 1 step ix was amended to include the following: "determining survival plasmid retention in cells by measuring the expression ratio of second's to first reporter gene".

However, Applicants point out that retention of the survival plasmid, as determined by its normalized fluorescence, traces a synthetic lethal condition. This is because under a synthetic lethal condition between for example, a chemical and a mutated gene of interest (pages 32-34), the cells selection for survival enforces maintenance of the naturally unstable survival plasmid (because it expresses the normal gene of interest) and thus the impairment of cell death. , . This is one embodiment of the invention, however, one skilled in the art is able to make other embodiments of the invention based on Applicants' disclosure.

Rejections under 35 USC §103 (a)

Claims 1-9 and 84-85 were rejected under 35 USC §103 (a) as being allegedly unpatentable over Deiss et al. (Science, vol. 252 pages 117-120, 1991) and Wade-Martins et al. (Nucleic Acid Research, vol. 27 number 7, pages 1674-1682, 1999). Specifically, the Examiner asserted that it would have been obvious to one skilled in the art to use GFP protein in the expression vector of Deiss et al.

In response, Applicants traverse the Examiner's rejection of claims 1-9 and 84-85 under 35 USC §103 (a) as allegedly being obvious over Deiss et al. in view of Wade Martins et al.:

Specifically, by combining the references, it would not have been obvious to one skilled in the art to obtain a method of screening molecules so as to identify a chemical compound or a drug that has a synthetic lethal property, when in combination with a gene of interest carrying a non-lethal mutation. In fact, based on the cited references, one skilled in the art could not obtain the subject matter defined by the claims. One skilled in the art upon reading Deiss et al. and Wade-Martins et al. would not be able to obtain Applicants' invention anymore had they not read Deiss et al. and Wade-Martins et al. The Examiner has not provided a *prima facie* case of obviousness based on Deiss et al. and Wade-Martins et al.

Applicants note that, the subject matter defined by the claims is directed to identifying a molecule which is a chemical compound or a drug that is synthetic lethal with a deficiency in a gene of interest. Synthetic lethal condition is recognized by the retention of a naturally unstable episome. Thus, the subject matter defined by the claims identify chemical compounds that are inhibitory to growth/survival/antiapoptotic genes that become lethal once presented to a cell harboring a synthetic/synergistic lethal mutant gene of interest. In contrast, Deiss et al. developed a method for identification of interferon triggered antigrowth/apoptotic genes. These genes are recognized by selection for the few cells which survive a lethal treatment (interferon addition) because the transfected antisense RNA has inactivated an antigrowth/apoptotic gene. Thus, Deiss et al. and the Applicant are aiming at different results and moreover using substantially different methods.

Further, there is no disclosure in Wade-Martins for the use of two GFP reporters genes, wherein the products of said first and second reporter gene have either different excitation peaks or different emission peaks. Specifically, Applicants have developed a highly sophisticated double-label fluorescent cell based assay, performed in microplates, where one variant GFP gene tags the episome while another variant GFP gene, which can be read in the same cell with the former GFP gene, is being carried out on an integrating plasmid vector. This method is not mentioned in neither Deiss nor in Wade-Martins. Moreover, incorporation of the GFP gene into the vectors described by Deiss would be of no advantage because as outlined above, the existence of a positive selection for cell survival would make the tracking of episomal DNA unnecessary and superfluous .

Therefore, it would not be obvious to a person of ordinary skill in the art, at the time the invention was made, to combine the disclosure of Deiss et al. and/or Wade-Martins so as to obtain the instant invention.

Moreover, by having a GFP marked episome capable of replicating in human cells and a method of generating/transfecting antisense human cDNA into Hela cells, one skilled in the art would not have been motivated to perform synthetic lethality for

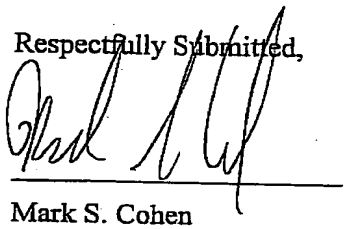
screening chemical compounds in human cells. Yet, even if one skilled in the art would have been motivated to combine the two references and substituting the cDNA library of Deiss with a group of chemical molecules, the result would have been relationships between stress (induced by interferon) and chemicals which inhibit antigrowth/apoptotic genes. . This result is substantially different from the results obtained in the Applicants' invention, which identifies chemicals that inhibit growth/antiapoptotic/survival genes which are synergistic lethal with a predefined mutated gene of interest.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection under 35 U.S.C. §103 (a).

Based on the foregoing, Applicants request allowance of the claims. Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below.

No fee is deemed necessary for filing this Amendment. However, if any fee is required, the undersigned Attorney hereby authorizes the United States Patent and Trademark Office to charge 05-0649.

Respectfully Submitted,



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